



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
GARY L. CLAYMAN

Serial No.: 08/758,033

Filed: November 27, 1996

For: METHOD AND COMPOSITION FOR
THE DIAGNOSIS AND TREATMENT OF
CANCER

Group Art Unit: 1632

Examiner: K. Hauda

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CERTIFICATE OF MAILING
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DECLARATION OF DR. JAMES A. MERRITT

BOX AF

Assistant Commissioner for Patents
Washington, D.C. 20231

I, James A. Merritt, declare that:

1. I am the Vice President of Clinical Affairs at Introgen Therapeutics, Inc., ("Introgen"), licensee of the above-captioned application, and have held this position for three years. I am an internist and board certified medical oncologist.

2. In this capacity, I regularly deal with cancer therapy clinical trials involving the use of p53 gene therapy. As such, I am familiar with the results from both Phase I and Phase II clinical studies being carried out by Introgen.
3. In the Phase I study reported in Clayman *et al.*, *J. Clin. Oncol.* 16:221-2232 (1998) (Exhibit 1), thirty-three patients with recurrent head & neck cancer were treated with intratumoral injections of Ad-p53. The treatment regimen consisted of at least one course of Ad-p53 (three times a week for two weeks). Of these, eighteen patients had non-resectable tumors (and received multiple treatment courses with two week rest between courses; continuing until disease progression or withdrawal of consent), permitting post-treatment assessment of tumor progression. Of these eighteen, twelve were p53+ by sequencing of tumor cell DNA. Of these twelve, two patients had greater than 50% tumor regression, four had stable disease, five had progressive disease, and in one the outcome of treatment could not be evaluated. By comparison, of the remaining six non-resectable patients, one was non-evaluable for p53 status. Of the five patients with mutated p53 genes, four exhibited progressive disease while two exhibited stable disease. (Of the total of 33 patients entered in the study, the remaining 15 underwent complete resection of their tumor three days after a single course of treatment, and could not be rigorously assessed for clinical response.)
4. In a subsequent Phase II trial (studies designated T201 and T202, analyzed February 26, 1999), 154 patients with recurrent, non-resectable head & neck

tumors were enrolled for Ad-p53 treatment on either (a) three consecutive (1, 2, 3), or (b) six biconsecutive (1, 3, 5, 8, 10, 12) days, with treatment cycles repeated every four weeks. One hundred forty-seven patients were treated, with 124 being evaluable. Of this latter group, two patients showed a complete response, two were partially responsive, and 24 exhibited stable disease for a period of three to seven months.

p53 status was ascertainable in 71 of these patients. Comparing clinical response to treatment on the basis of p53+ and p53- status (as determined by DNA sequencing), the following results were obtained:

SUMMARY OF PHASE II CLINICAL DATA BY p53 STATUS (n=71)

p53 status*	CR	PR	SD	PD	NE
p53+	0	2	6	21	3
p53-	0	1	6	27	5

* as determined by sequencing of exons 1-10; some patients had unknown p53 status.

CR – complete response; PR – partial response; SD – stable disease; PD – progressive disease; NE – non-evaluable

5. These results demonstrate that treatment of p53+ tumors using a p53-expressing vector is at least as clinically useful as treatment of tumors that lack a wild-type p53 molecule.
6. I declare that all statements made herein of my own knowledge are true, and that all statements of my own belief are believed to be true, and further that these statements were made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this patent, and any reexamination certificate issuing thereon.

Date

25 August 1999

Dr. James A. Merritt

